# Vitamin Substitution Beyond Childhood—Requirements and Risks

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Abstract: BACKGROUND Vitamins are vitally important, but they are not always adequately supplied with the diet. In this review, we present the advantages and disadvantages of vitamin supplementation and the indications for it in various life situations. METHODS This review is based on pertinent publications retrieved by a selective search of the literature. RESULTS The German National Nutrition Survey II (Nationale Verzehrsstudie II) showed that most people in Germany consume adequate amounts of vitamins in their diet, with the exception of vitamin D and folate. Supplements are often taken by adults who already consume a balanced diet. Depending on the vitamin, 3-13% of survey respondents took vitamin supplements; the ones most often taken were vitamins C and E. No convincing evidence has yet demonstrated a health benefit from vitamin supplementation in addition to a balanced diet for the primary prevention of nutrition-associated diseases. Vitamin supplementation is indicated in certain specific life situations, e.g., pregnancy, but otherwise unnecessary, unless a deficiency has been diagnosed or the individual is at elevated risk. CONCLUSION Vitamin supplementation is recommended for certain population groups: folic acid for pregnant women, vitamin B12 for vegans and persons with resorption disorders, vitamin D for persons with insufficient endogenous synthesis. In all other cases, it should first be tested whether the individual might be substantially helped by dietary changes alone. In general, the potential adverse effects of vitamin supplementation need to be considered, and its benefits weighed against its risks.

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Continuing Medical Education

# Vitamin Substitution Beyond Childhood

## Requirements and Risks

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## Summary

Background: Vitamins are vitally important, but they are not always adequately supplied with the diet. In this review, we present the advantages and disadvantages of vitamin supplementation and the indications for it in various life situations.

Methods: This review is based on pertinent publications retrieved by a selective search of the literature.

Results: The German National Nutrition Survey II *(Nationale Verzehrsstudie II)* showed that most people in Germany consume adequate amounts of vitamins in their diet, with the exception of vitamin D and folate. Supplements are often taken by adults who already consume a balanced diet. Depending on the vitamin, 3–13% of survey respondents took vitamin supplements; the ones most often taken were vitamins C and E. No convincing evidence has yet demonstrated a health benefit from vitamin supplementation in addition to a balanced diet for the primary prevention of nutrition-associated diseases. Vitamin supplementation is indicated in certain specific life situations, e.g., pregnancy, but otherwise unnecessary, unless a deficiency has been diagnosed or the individual is at elevated risk.

Conclusion: Vitamin supplementation is recommended for certain population groups: folic acid for pregnant women, vitamin $B_{12}$ for vegans and persons with resorption disorders, vitamin D for persons with insufficient endogenous synthesis. In all other cases, it should first be tested whether the individual might be substantially helped by dietary changes alone. In general, the potential adverse effects of vitamin supplementation need to be considered, and its benefits weighed against its risks.

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According to a meta-analysis, the risk of cardiovascular diseases and overall mortality are inversely related to the consumption of fruit and vegetables, with the lowest risk seen at 800 g/day (1). This finding has been attributed to the vitamin and mineral content of fruit and vegetables, among other explanations (1). Other foods are also rich in certain vitamins, such as whole grains (vitamins $B_1$, $B_6$), milk and dairy products (vitamins A, $B_2$, $B_{12}$), eggs (vitamins A, D), meat (vitamins A [liver], $B_1$, $B_2$, $B_3$, $B_6$, $B_{12}$), fish (vitamins $B_3$, $B_6$, $B_{12}$, D), nuts (vitamin $B_3$, biotin, vitamin E), and oils and fats (vitamin E) (2). How do we meet our need for vitamins if we cannot eat these foods, or choose not to eat them? When is the supplementation of certain nutrients advisable for a generally healthy adult?

## Learning objectives

Having read this article, the reader should

- know about vitamin intake and vitamin supplementation behavior in the German population,
- be able to name critical nutrients and risk groups,
- know the motives of those who take vitamin supplements and their possible benefits and harms.

By "supplementation", we mean the taking of vitamins as over the counter products for a specific and supplementary ingestion of vitamins in addition to the amount consumed with the diet. The consumption

**Lower cardiovascular risk**

The consumption of 800 g of fruit and vegetables per day is associated with the lowest risk of cardiovascular diseases and overall mortality, according to a meta-analysis.

**Vitamin-rich foods, apart from fruit and vegetables:**

Whole grains (vitamins $B_1$, $B_6$),
milk/dairy products (vitamins A, $B_2$, $B_{12}$), eggs (vitamins A, D), meat (vitamins A [liver], $B_1$, $B_2$, $B_3$, $B_6$, $B_{12}$),
fish (vitamins $B_3$, $B_6$, $B_{12}$, D), nuts (vitamins $B_3$, E, biotin),
oils and fats (vitamin E)

of nutrient-enriched foods, e.g., so-called ACE juices, is not covered by the term.

## Methods

This review is based on pertinent publications retrieved by a selective search of the literature. The websites of relevant institutions were searched for reference values for nutrient intake. Representative national studies were used to characterize nutrient intake in the German population and among supplement users; non-representative studies were used as well to characterize nutrient intake in risk groups. As for the putative effectiveness of supplementation for primary prevention, a literature search was carried out in PubMed and the Cochrane Library, with the key words "vitamin supplementation AND (prevention OR risk)". Emphasis was laid on systematic reviews, particularly those of the Cochrane Collaboration.

## Definitions of terms

The terms used in this article are defined in the *Box*.

## Vitamin intake via foods and supplements in Germany

The representative German National Nutrition Survey II (*Nationale Verzehrsstudie II,* NVS II; 2005–2007; 15 371 participants) showed that the median vitamin intake of adults living in private households in Germany met the published reference values for nutrient intake of the German-speaking countries (Germany, Austria, and Switzerland), with the exception of folate and vitamin D. In total, 79% of men and 86% of women took less than the daily recommended amount of folate (400 µg folate equivalent per day) (3). Folic acid is the synthetic form of folate that is present in supplements and vitamin-enriched foods. Because folic acid and folate are absorbed and used differently by the body, the reference values are given in folate equivalents, where 1 µg of folate equivalent corresponds to either 1 µg of folate or 0.5 µg of folic acid (2). Concerning, vitamin D, 82% of men and 91% of women consumed less than the amount that was recommended at the time of the study, namely, 5 µg per day for persons under age 65 years, and 10 µg for those aged 65 years and above (3). The current reference values for adults are 300 µg of folate equivalents and 20 µg of vitamin D per day; the latter figure is applicable only to persons with inadequate endogenous synthesis (2). Vitamin D is not a vitamin in the classical sense, because it can be synthesized in adequate amounts in the body itself, as long as the skin is exposed to sufficient UVB light (2).

Overall, 24% of the NVS II participants were taking nutrient supplements (30% of women, 19% of men) (4). Supplement intake was most common among women aged 65 to 80 years (46%); 30% of men in this age group also took supplements (4). Depending on the respective vitamin, 3–10% of men and 4–13% of women reported the use of supplements; those most frequently taken were vitamins C and E (4). On average, supplement users consumed 50–100% of the reference values for the German-speaking countries for vitamins $B_3$, C, D, E, and folate through supplementation alone (3, 4). As a result, supplement users in the NVS II, in the median, achieved or exceeded the reference value for all vitamins studied in the NVS II, when their entire consumption (dietary intake plus supplementation) was taken into account (4). For a number of B vitamins ($B_1$, $B_2$, $B_3$, $B_6$) and in some age groups, the daily supplement intake exceeded the reference values all by itself (3). The same was true for the intake of vitamin A in retinol equivalents (men aged 14 to 18 years) and vitamin E in tocopherol equivalents (women aged 65 to 80 years) (3). The reference values for vitamins A and E, like those for folate, are stated in equivalent amounts, because of the differing physiological activity of the various vitamin A and vitamin E compounds: thus, 1 mg retinol equivalent corresponds to 1 mg of retinol, 6 mg of all-trans-β-carotene, or 12 mg of other provitamin A carotenoids (2). For vitamin E, 1 mg of RRR-α-tocopherol equivalent corresponds, for example, to 1.1 mg of RRR-α-tocopheryl acetate, 2 mg of RRR-β-tocopherol, 4 mg of RRR-γ-tocopherol, or 3.3 mg of RRR-α-tocotrienol (2). Note that the NVS II probably underestimated vitamin E intake because of the food nutrient database that was employed, which primarily took account of α-tocopherol (4).

The German Federal Institute for Risk Assessment (*Bundesinstitut für Risikobewertung,* BfR) has determined that vitamin A supplementation confers a high risk of exceeding the upper intake level (UL) of vitamin A. If the reference value is chronically exceeded, there is a risk of an over-supply with the respective nutrient. At present, however, there are no obligatory upper limits (on either the national or international regulatory level) for vitamin quantities in nutritional supplements. According to the BfR, the European Union is currently preparing regulations stipulating the maximum quantities of vitamins and minerals (5).

## Risk groups and critical nutrients, with consideration of biomarkers

As intake data alone are insufficiently informative about a person's vitamin status, biomarkers should also be considered. The vitamins frequently regarded as particularly critical are vitamin $B_{12}$, vitamin D, and folate. In this connection, the representative German Health Interview and Examination Survey for Adults

**Reference values**

The median vitamin intake of adults living in private households in Germany meets the published reference values for nutrient intake of the German-speaking countries, with the exception of folate and vitamin D.

**The risks of supplementation**

The consumption of vitamin supplements in addition to a balanced diet can lead to a vitamin intake that is markedly higher than the reference value.

BOX

### Definition of terms

- Inadequate vitamin supply: the quantity of a vitamin ingested by the individual does not meet his or her needs. Intake in an amount below a published reference value does not necessarily imply inadequate supply or a state of deficiency or insufficiency, although it does elevate the risk of a suboptimal vitamin supply. The reference values incorporate a safety margin to meet the needs of approximately 98% of the normal population while maintaining body reserves (2). On the other hand, vitamin status can be inadequate even if the vitamin is ingested in an amount equal to the reference value, as a consequence of metabolic changes or diseases.
- Sufficient/adequate vitamin status: the biomarkers of the vitamin are within established limits, and there are no manifestations of a deficient state.
- Vitamin deficiency: there are clinical manifestations caused by a deficient status of the respective vitamin, or the biomarkers of the vitamin are below the established limits.
- Hypervitaminosis: there are pathological manifestations due to an intake of the vitamin that is acutely or chronically much higher than the individual requirement (excessive supply).
- Tolerable upper intake level (UL): the maximal daily intake of a nutrient from all sources which, even if chronically maintained, would not be expected to have any adverse effect on health.

(*Studie zur Gesundheit Erwachsener in Deutschland,* DEGS) revealed that the serum concentration of 25-hydroxyvitamin-D (a vitamin D status parameter) was less than 30 nmol/L, indicating a deficiency, in approximately 30% of the population (6). On the other hand, 38% of the population had a concentration of 50 nmol/L or more (6), which is recommended for the prevention of musculoskeletal disorders (7, 8). The serum concentration of folate was adequate in 86% of the population, i.e., at least as high as the reference value of 4.4 ng/mL defined in the study (9). As for vitamin $B_{12}$ status in Germany, no representative data are yet available from studies that investigated not just the serum concentration of vitamin $B_{12}$, but also functional parameters, such as methylmalonic acid.

In the *Table,* we provide an overview of vitamin $B_{12}$, vitamin D, and folate with respect to status parameters, reference values, deficiency diseases/hypervitaminoses, and recommendations about dietary intake and supplementation. A basic point is that clinically manifest vitamin deficiencies are rare in Germany. If such a state is suspected, biomarkers should be measured, but there is no indication for the routine laboratory measurement of vitamin biomarkers in persons who are not at elevated risk.

#### Pregnant and breastfeeding women

Pregnant and breastfeeding women need most vitamins in higher amounts than women who are neither (2). A mixed diet can meet the need for all vitamins, except for folate and vitamin D. There is, however, no evidence to suspect an inherently higher vitamin D requirement because of pregnancy or breastfeeding.

Increased folate intake is recommended even before a woman becomes pregnant: women who want to become pregnant, or who might do so, should take supplementary folic acid (400 µg/day) starting no later than four weeks before the beginning of pregnancy and until the end of the first trimester, to reduce the risk of a neural tube defect in the child (10, 11). Alternatively, other folate compounds (calcium-L-methylfolate, 5-methyltetrahydrofolic acid-glucosamine) can be taken at the equivalent dose (10). Many women take multivitamin preparations in pregnancy (12). Meta-analyses have shown that the daily intake of folic acid, either as a single preparation or in combination with other vitamins and/or minerals, lessens the relative risk of neural tube defects by 69% (13).

In the VitaMinFemin study, 78% of pregnant women and 54% of women who were not pregnant had a 25-hydroxyvitamin-D serum concentration below 50 nmol/L (14). Pregnant women who are rarely out in the sun, or who largely cover their skin or use sunscreens when in the sun, as well as women with dark skin, should take a daily supplement with 20 µg of vitamin D (10).

#### The elderly

Human aging is often associated with a decrease in total energy expenditure, which is largely due to diminishing physical activity (15). Hardly any robust data on micronutrient requirements in old age have been published to date. Frequently, the reference values used for the elderly are those that are stated for younger adults or are extrapolated accordingly. As a result, elderly persons face the challenge of how to take in roughly the same quantity of vitamins in a smaller total amount of food.

In advancing age, folate and the vitamins $B_{12}$ and D are considered as critical nutrients. However, advancing age is not inevitably accompanied by vitamin deficiency: in the follow-up period of the Longitudinal Study on Nutrition and Health Status in Senior Citizens in Giessen (*Giessener Senioren Langzeitstudie,* GISELA), which included persons aged 60 years and

**Pregnant women**

Women who can or want to become pregnant should take 400 µg of folic acid supplement per day.

**The elderly**

Vitamin D, vitamin $B_{12}$, and folate are critical vitamins for the elderly. If a deficiency state is suspected, the vitamin status should be checked and supplementation should be given as needed.

**TABLE**

**An overview of critical vitamins[*1]**

| Vitamins and the corresponding deficiency states | Status parameters and threshold values for adults | Recommended daily intake | Food sources | Overdose (adults) | Recommendations for supplementation (adults) |
|---|---|---|---|---|---|
| **Vitamin D** | | | | | |
| deficiency<br>• rickets (in children)<br>• osteomalacia (in adults)<br><br>persistent insufficiency<br>• osteoporosis<br><br>manifestations (in adults)<br>• impaired bone mineralization<br>• diffuse bone and muscle pain, muscle weakness (myopathy)<br>• fractures | serum concentration of 25-hydroxyvitamin D (nmol/L)<br>• <30 = deficient<br>• 30 to <50 = insufficient<br>• ≥ 50 = adequate<br>• >200 = excessive (debated) | for adults:<br>• 20 µg/day (if endogenous synthesis is insufficient[*2]) | • fatty fish (e.g., salmon, herring)<br>• eggs | upper intake level (UL) = 100 µg/day<br><br>potential adverse effects of overdose:<br>• hypercalcemia<br>• renal disease<br>• gastrointestinal symptoms | general<br>• supplementation for deficient or insufficient state documented by a vitamin status determination<br>• dose: 20 µg/day (higher quantities of intake may be medically indicated)<br><br>if endogenous synthesis is insufficient[*2]<br>• dose: 20 µg/day is recommended even if no vitamin status determination has been performed |
| **Vitamin $B_{12}$** | | | | | |
| • megaloblastic anemia<br><br>• neurological dysfunction (e.g., myelopathy, neuropathy, neuropsychiatric disturbances, optic nerve atrophy, dysesthesiae, depression, memory impairment) | the total vitamin $B_{12}$ concentration or the holotranscobalamin concentration should be measured in combination with methylmalonic acid or homocysteine[*3] | for adults:<br>• 4 µg/day<br><br>for pregnant women:<br>• 4.5 µg/day<br><br>for breastfeeding women:<br>• 5.5 µg/day | • meat<br>• fish<br>• seafood<br>• eggs<br>• dairy products | UL = not determined<br><br>potential adverse effects of overdose:<br>• no adverse consequences for health due to excessive intake have yet been described in healthy persons | • for documented deficiency<br>• regular monitoring of persons at risk<br>• in atrophic gastritis, malabsorption, veganism<br>• dose: 4–5.5 µg/day (higher quantities of intake may be medically indicated; in particular, in case of malabsorption, 1 mg/day can be given) |
| **Folate** | | | | | |
| • megaloblastic anemia<br>• neural tube defect (neonates) | folate should be measured both in serum/plasma and within erythrocytes<br><br>serum/plasma concentration (nmol/L) (in repeated measurements)<br>≤ 6.8 = deficient<br>≥ 10 = adequate<br><br>concentration within erythrocytes (nmol/L)<br><317 = deficient<br>≥ 340 = adequate | folate equivalents<br><br>for adults:<br>• 300 µg/day<br><br>for pregnant women:<br>• 550 µg/day<br><br>for breastfeeding women:<br>• 450 µg/day | • green leafy vegetables<br>• legumes<br>• tomatoes<br>• oranges<br>• nuts<br>• whole-grain products | UL = 1 mg folic acid per day<br><br>potential adverse effects of overdose:<br>• there is concern over possible induction of proliferation of neoplastic foci, as well as adverse effects of unmetabolized folic acid in the blood | for women of childbearing age who could, or want to, become pregnant<br>• 400 µg/day in addition to the recommended dietary intake (at least 4 weeks before the beginning of pregnancy and throughout the first trimester)<br><br>general<br>• supplementation for deficient state documented by a vitamin status determination<br>• the daily dose should equal the reference value |

[*1] This table is based on the recommendations of the European Food Safety Authority (EFSA) (7, 23, e16), and the Nutrition Societies of Germany, Austria and Switzerland (2).

[*2] Endogenous vitamin $D_3$ synthesis is largely determined by the UVB exposure of the skin. Persons with light skin who live in the temperate climate at mid-latitudes can cover their needs with 5 to 15 minutes of exposure of the hands, arms, and face to sunlight between 10 am and 3 pm on two to three days per week (e14, e15), as long as they do not use a sunscreen during this time. Measures should be taken to protect the skin and eyes (sunscreen lotion, sunglasses with UV protection) if there is any longer exposure to sunlight, because of the risk of cancer.

[*3] Total vitamin $B_{12}$ (pmol/L): <148 = deficient; 148 to 221 = insufficient; >221 = adequate (debated)
Holo-transcobalamin (pmol/L): <8.4 = probably deficient (debated); 8.4 to <20 = possibly deficient (debated); ≥ 38 = adequate (debated)
Methylmalonic acid (nmol/L): > 840 = deficient (debated); >350 to <840 = insufficient (debated); <210 / <270 = adequate (debated)
Homocysteine (µmol/L): <12 = adequate

older, increasing age was not found to have a negative impact on, e.g., B-vitamin biomarkers (16, 17).

As for vitamin D, the DEGS revealed an increasing prevalence of suboptimal vitamin D status with advancing age (6). This is mainly attributed to a reduced vitamin D synthesizing ability of the skin, reduced exposure to sunlight, and age-associated changes in body composition (18). In the Cooperative Health Research in the Region of Augsburg (KORA) age study, 52% of the participants (aged 65–93 years) had a 25-hydroxyvitamin-D concentration below 50 nmol/L (19); the corresponding figure in the GISELA study was only 19% (18). This shows that older adults are indeed able to achieve a 25-hydroxyvitamin-D concentration of 50 nmol/L or above, particularly in the summer and autumn season, provided they follow an active lifestyle (18). However, in accordance with the DEGS study, a decrease in the serum concentration of 25-hydroxyvitamin-D with advancing age was also observed in the GISELA study (20). For persons with inadequate endogenous synthesis, supplementation of 20 µg/day is recommended.

Resorption disorders, diseases such as atrophic gastritis and pernicious anemia, and drugs such as proton-pump inhibitors can promote low serum concentrations of vitamin $B_{12}$ in the elderly. If so, oral supplementation of 1000 µg/day is recommended, as the absorption rate via passive diffusion is approximately 1% (21). In the GISELA study, 17% of the elderly participants had a serum vitamin $B_{12}$ concentration of 148 pmol/L or less (22). In the KORA age study, 27% of the participants aged 65 years and above had an inadequate level of vitamin $B_{12}$, defined as a concentration below 221 pmol/L (19). However, the assessment of vitamin $B_{12}$ status by its serum concentration alone must be viewed critically (23, 24).

Folate deficiency, too, is more common in old age (25), mainly because of inadequate intake of folate-rich food. In the GISELA study, 8% of the participants had folate concentrations below 10 nmol/L (17); in the KORA age study, 9% had concentrations below 13.6 nmol/L (19). Evidence suggests that folic acid supplementation can promote the development and progression of malignant lesions that are already present (26, 27). Therefore, general supplementation in all elderly persons, even those who do not have a documented folate deficiency, is not recommended.

Compared to healthy elderly persons who are still able to live independently, elderly persons in care homes and nursing homes are at higher risk of vitamin deficiency. A study from Spain and Argentina, for example, showed that, even in the late summer, more than 80% of the elderly persons in nursing homes who were studied had a 25-hydroxyvitamin-D concentration of less than 50 nmol/L (28). A German study showed that the intake of numerous vitamins, mainly vitamins C, D, and E and folate, was below the reference values (29). The early detection of malnutrition and undernutrition by the nursing staff and the initiation of appropriate treatment measures are important goals.

### Vegans and vegetarians

The more one restricts one's food intake, and the less varied the diet, the higher the risk of inadequate intake of one or more vitamins. Vegetarians who consume dairy products and eggs can still keep up a well-balanced diet; but, if all foods of animal origin are avoided, as in a vegan diet, the requirements for certain vitamins cannot be met by the consumption of non-vitamin-enriched foods alone. This concerns vitamin $B_{12}$ above all, which needs to be supplemented regularly in the amount of the reference value. Vitamins $B_2$ and D can also be problematic. Adequate vitamin $B_2$ intake can be achieved by the deliberate consumption of vegetable foods that are rich in vitamin $B_2$, e.g., vegetable oil seeds, nuts, and whole grains. Vitamin D supplementation of 20 µg/day is recommended for persons with inadequate endogenous synthesis (30).

The German Nutrition Society and the nationwide "Gesund ins Leben" network (*Healthy Start—Young Family Network*) advise against a vegan diet for pregnant and breastfeeding women (10, 30). While it is true that the available data on the health risks of a vegetarian or vegan diet for mother and child do not yet permit any definite conclusion, an elevated risk of vitamin $B_{12}$ deficiency is nonetheless evident (30).

Individual evaluation is important as a component of dietary counseling (30, 31). Persons who follow a vegan diet, or a vegetarian diet without dairy products or eggs, should have their vitamin $B_{12}$ status regularly checked. If a deficiency is found, the patient should first be given 1 mg of oral vitamin $B_{12}$ (in the form of either cyanocobalamin or hydroxycobalamin) and then supplementation in the amount of the reference value, under continuous monitoring (21).

## Characterization of vitamin supplement users in Germany

The Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC), with approximately 25 000 participants, indicated that supplement users, compared to non-users, have a

**Vegans**

Vitamin $B_{12}$ supplementation, either with vitamin-enriched foods or with a vitamin supplement, is essential for persons who follow a vegan diet.

**Vitamin supplementation**

At present, health benefits of a vitamin supplementation for the primary prevention of nutrition-associated diseases have not yet been confirmed beyond doubt in adults without vitamin deficiency.

higher education level and a more healthful lifestyle and diet (32). In the NVS II as well, supplements were mainly taken by persons who already had a good intake of nutrients and a balanced diet (33).

In a longitudinal study of part of the NVS II cohort (NEMONIT 2008–2012/2013), the motivations most commonly mentioned for taking vitamin supplements were prevention of nutritional deficiencies and health problems, general well-being, and treatment of nutritional deficiencies and diseases. Participants who predominantly reported prevention as their motivation had a more balanced diet and were more physically active than participants who did not take supplements. On the other hand, participants who stated treatment as their main motivation were older and had a poorer self-assessed health state than non-users of supplements (34).

## Vitamin supplementation for primary prevention: health benefits

In general, when a vitamin deficiency is manifestly present, supplementation of the deficient nutrient is advisable. It is questionable, however, whether and to what extent the use of supplements by persons without such deficiencies might benefit their health.

Two recently published systematic reviews investigated the possible efficacy of vitamin supplements in the prevention of cardiovascular diseases and mortality using randomized, controlled trials. No significant effect was found for multivitamin preparations, the vitamins A, $B_3$, $B_6$, C, D, and E and the provitamin beta-carotene (35, 36). Folic acid reportedly lowered the relative risk of cardiovascular diseases by 17% (35) and that of stroke by 20% (35, 36) This finding, however, was primarily based on the results of a single trial, the China Stroke Primary Prevention Trial (CSPPT), in which the efficacy of folic acid supplementation to prevent stroke in hypertensive persons in China was studied (37). The authors of both studies attributed the benefit of folic acid supplementation to the lack of vitamin-enriched food in China (35, 36).

In 2017, it was concluded, in a systematic review of the putative effects of nutrient supplements on cardiovascular diseases, cancer, and mortality, that vitamin E supplements lead to a 12% relative reduction of cardiovascular mortality, and folic acid supplements to a 19% relative reduction of the incidence of cardiovascular diseases (38). The latter finding, however, was also primarily attributable to the results of the CSPPT. In contrast, supplementation with vitamin C, D, or K did not lower the risk of any of the outcomes studied (38). Nor did a review by the Cochrane Collaboration detect any benefit from vitamin C supplementation (with a single-agent preparation) with respect to cardiovascular diseases in either healthy persons or persons at risk (39). In two further meta-analyses, the intake of folic acid supplements was not found to be associated with cancer incidence (40, e1).

In 2014, the Cochrane Collaboration found an apparent relative risk reduction of overall mortality (−3%) and cancer mortality (–12% for vitamin $D_3$) through vitamin D supplementation (e2). Likewise, in 2019, another meta-analysis indicated that vitamin D led to a relative risk reduction of cancer mortality (–16%) but had no significant effect on overall mortality (e3). It is, above all, vitamin $D_3$ that seems to have the potential of lowering the risk of overall mortality and cancer mortality; vitamin $D_2$, alfacalcidol and calcitriol apparently do not have this property (e2). Vitamin D, combined with calcium, also led to a 16% relative reduction in the risk of hip fractures in the elderly (e4). At present, there is inadequate evidence to judge the possible extraskeletal effects of vitamin D conclusively, although there are multiple indications that a low vitamin D status is a consequence, rather than a cause, of extraskeletal chronic diseases (e5).

Vitamin supplementation has not been shown to confer any relevant protection against age-dependent macular degeneration (e6) or to preserve cognitive abilities to a statistically significant extent in middle-aged and elderly persons (e7).

In summary, the overall state of the evidence on the putative preventive effects of vitamin supplementation is inconsistent. Because of this, and the fact that the evidence studied in the systematic reviews was generally rated as being of low to moderate quality, no recommendation can be given for the use of vitamin supplements to prevent nutrition-associated diseases.

## Possible adverse effects of vitamin supplementation

Most of the current systematic reviews have not revealed a significantly elevated risk of chronic diseases or death as a consequence of taking nutritional supplements (35, 36). In an intervention trial in Finland, however, smokers who took beta-carotene as a supplement were found to develop lung cancer at a higher rate over the ensuing years than those who took a placebo instead; this finding was the opposite of the protective effect that had been expected *a priori* (e8). It was likewise concluded in a recent systematic review that high-dose beta-carotene

**Adverse effects on health**

The risk of adverse effects on health is higher when vitamin supplements are taken in amounts that lead to an exceedance of the upper intake level.

**Vitamin A and beta-carotene**

Vitamin A and beta-carotene should be supplemented only when medically necessary.

supplementation in current and former smokers increases the risk of lung cancer (e9). A systematic review of data from nearly 300 000 participants showed that persons who took antioxidants had a 3% higher relative risk of premature death, compared to those who took placebo (e10). The increased mortality was seen mainly among persons who took beta-carotene and vitamin E; the results were less clear for vitamin A, and vitamin C was not found to have any effect at all (e10). A further analysis, taking account of the supplement doses and the quantities consumed per day, led to the conclusion that the increased mortality was attributable to the use of high-dose supplements, i.e., those taken in amounts greater than the reference values for recommended daily intake (e11). The effects of supplementation in amounts near the reference value remain unclear (e11). In a review already mentioned above, the use of vitamin A supplements was found to be associated with a 16% relative elevation of the risk of cancer, while the use of beta-carotene supplements in a single-agent preparation was associated with a 6% relative elevation of overall mortality (38). Vitamin D supplements combined with calcium reportedly led to relative risk elevations of gastrointestinal symptoms (+5%) (e4), renal diseases (+16% and +17% in separate studies) (e2, e4), and stroke (+17%) (36). There is some evidence that folic acid supplements can promote the development and progression of malignant lesions that are already present (27, e12), but the study findings on this point are inconsistent (40, e1, e13).

Apart from the risk of over-supply, potential interactions between nutritional supplements and drugs must be considered. Vitamin K, for example, can interact with coumarin anticoagulants and in consequence, lower their effectiveness (5). In view of this fact, a comprehensive medical history should be taken before vitamin supplementation is recommended to any patient.

**Conflict of interest statement**
The authors state that they have no conflict of interest.

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**No general recommendation**

Vitamin supplementation for the prevention of nutrition-associated diseases cannot be generally recommended.

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► **Supplementary material**

**For eReferences please refer to:**
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Only one answer is possible per question. Please select the answer that is most appropriate.

### Question 1

**What disease due to vitamin deficiency can arise in adults as the consequence of either folate or vitamin $B_{12}$ deficiency?**

a) rickets
b) megaloblastic anemia
c) myopathy
d) neural tube defect
e) osteomalacia

### Question 2

**What vitamin supplement is generally recommended for use by pregnant women?**

a) vitamin E
b) vitamin $B_1$
c) folic acid
d) vitamin C
e) vitamin $B_6$

### Question 3

**What vitamin supplement should be taken by persons following a vegan diet?**

a) vitamin $B_1$
b) vitamin K
c) vitamin $B_6$
d) vitamin $B_{12}$
e) vitamin C

### Question 4

**Ideally, when should a woman who wants to become pregnant begin taking a folic acid supplement?**

a) no later than four weeks before conception
b) at the time of conception
c) at the end of the first trimester
d) at the end of the second trimester
e) never; pregnant women do not need folic acid supplementation

### Question 5

**What is the main cause of vitamin $B_{12}$ deficiency in the elderly?**

a) diminished intestinal synthesis of vitamin $B_{12}$
b) inadequate exposure to sunlight
c) low consumption of fruit and vegetables
d) atrophic gastritis
e) low consumption of milk

### Question 6

**What is a main reason why vitamin D deficiency is more common in the elderly than in younger persons?**

a) lower meat consumption
b) enhanced degradation of vitamin D metabolites
c) low intestinal absorption of vitamin D
d) more common use of proton pump inhibitors
e) lower ability of the skin to synthesize vitamin D

### Question 7

**What vitamins are considered critical nutrients in old age?**

a) vitamin $B_{12}$, vitamin D, and folate
b) vitamins D and E
c) vitamins C and E
d) vitamins $B_{12}$, D, and $B_1$
e) vitamins A, C, and E

### Question 8

**The combined intake of what two substances has been found, in systematic reviews, to be associated with an elevated risk of gastrointestinal symptoms, kidney diseases, and stroke?**

a) vitamin E and iron
b) vitamin A and zinc
c) vitamin B and magnesium
d) vitamin D and calcium
e) vitamin C and folic acid

### Question 9

**Which of the following is true of people who take nutritional supplements?**

a) They often perform shift work.
b) They often have a low educational level.
c) They are less well supplied with nutrients than the general population.
d) They are usually under 35 years old.
e) They tend to have a more healthful lifestyle than non-users.

### Question 10

**What nutrient was found, in an interventional study on smokers, to be associated with an elevated risk of lung cancer?**

a) vitamin D
b) vitamin $B_6$
c) beta-carotene
d) vitamin C
e) folic acid

► **Participation in the CME certification program is possible only over the Internet: cme.aerzteblatt.de**

**Supplementary material to:**

# Vitamin Substitution Beyond Childhood

Requirements and Risks

by Alexandra Jungert, Katharina Quack Lötscher, and Sabine Rohrmann

Dtsch Arztebl Int 2020; 117: 14–22. DOI: 10.3238/arztebl.2020.0014

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